REMARKS

Applicants respectfully request reconsideration of this application, and reconsideration of the Office Action dated August 26, 2004. Upon entry of this Amendment, claims 1-5, 7, 9-11, and 21-24 will remain pending in this application. The changes to the claims are fully supported by the specification and original claims. For example, the changes to claim 1 are supported at *inter alia* page 15; page 16, lines 1-6 and lines 16-24; page 17, lines 13-15; pages 18, 20, and 21 and Figures 1 and 2. No new matter is incorporated by this Amendment.

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The specification is objected to and claims 1-7, 9, 21, 23, and 24 are rejected under 35 U.S.C. § 112, first paragraph, for purportedly failing to provide an enabling disclosure. Specifically, the Office Action asserts the specification does not adequately define "natural biotin", "linkers", "a trifunctional crosslinking moiety" and "derivatives or fragments thereof having essentially the same binding function to biotin as avidin or streptavidin." Applicants respectfully traverse.

As an initial matter, Applicants point out the claims have been amended to refer to "biotin" instead of "natural biotin." Applicants submit that those of skill in the art readily understand what biotin is. Moreover, since those of ordinary skill in the art would readily know what biotin, avidin and streptavidin are and how these molecules interact, those of ordinary skill also would readily understand what is intended by "derivatives or fragments thereof having essentially the same binding function to biotin as avidin or streptavidin." Furthermore, Applicants further submit that those of ordinary skill in the art would readily understand what is intended and encompassed by the terms "linkers" and "a trifunctional crosslinking moiety." However, Applicants note that claim 1 has been amended to further define the term "linker."

Applicants point out that the specification is not required to teach that which is known to those of skill in the art. Moreover, "[a]n applicant is not required to describe in the specification every conceivable and possible future embodiment of his invention." *Rexnord Corp. v. Laitram Corp.*, 274 F.3d 1336, 1344 [60 USPQ2d 1851] (Fed. Cir. 2001). In addition, "a specification may, within the meaning of 35 U.S.C. § 112 para. 1, contain a written description of a broadly claimed invention without describing all species that [the] claim encompasses." *Utter v. Hiraga*, 845 F.2d 993, 998 [6 USPQ2d 1709] (Fed. Cir. 1998). However, even with the above case law in mind, Applicants submit that the specification more than adequately teaches how to make and use the claimed invention.

The claimed method concerns the conditioning of a device by a reagent having two biotins attached to the reagent, which during the conditioning becomes attached to one avidin in the device, whereby a highly stable multipurpose extracorporeal toxic binding device is produced.

Example 1 teaches how to produce a dibiotin compound, containing two biotin moieties, one type of linkers (a and b) and the trifunctional cross-linking moiety (i.e. 4,7,10-trioxa-l,13-trideeanediamine), wherein the distance between the biotins and the trifunctional cross-linking moiety is 31Å. Through this particular example it is possible for a skilled artisan to produce other dibiotin compounds with different linkers having different lengths providing that the lengths are such that the two biotins in the dibiotin compound will bind to the same immobilized avidin/streptavidin molecule, and to apply different trifunctional cross-linking moieties.

Example 2 teaches how to conjugate a toxin binding moiety to the dibiotin compound, produced in example 1. The toxin binding moiety is an antibody. However, a person skilled in the art would know how to attach other toxin binding moieties, such as attaching a third biotin molecule without undue experimentation, by combining examples 1 and 2.

Example 3 teaches how to condition an avidin column with a dibiotin compound. In this particular case the reagent consists of three biotin molecules. The example gives rise to an avidin coated column, which through the conditioning results in two biotins being attached to one avidin. This gives rise to a specific, organized network, which is important to establish for further use of the column in clearing blood from toxic binding molecules.

Applicants submit examples 1-3 are more than sufficient for establishing the claimed method and use the method for conditioning a specific biotin binding device to a multipurpose extraeorporeal device (i.e. to convert an extracorporeal device which prior to this conditioning is limited to the removal of biotinylated exogenous agents, but after the conditioning is capable of removing specific endogenous agents from the blood circulation).

Further examples show how the conditioned device may be used. Example 4 discloses the removal of antibodies from the blood flow by the use of a device being conditioned by the inventive method. The antibodies without any biotin are removed through binding to a toxic binding moiety. Moreover, Example 5 discloses the removal of streptavidin/avidin toxic compounds (no biotin attached to the toxic compound) by passing the toxic compound through a conditioned device which has been conditioned using a biotin trimer.

With all due respect, Applicants would gently remind the Examiner that the basis for raising the enablement statute is for instances where the specification fails to provide sufficient guidance to one of ordinary skill in the art to practice the invention within the scope of the claims without undue experimentation. The claimed method involves processes and steps that are considered predictable. The materials are known. There are demonstrative examples to guide the skilled practitioner through the various elements to accomplish the claimed method.

The Office Action has raised no substantial evidence or analysis to challenge the presumption of enablement. To maintain this rejection, the Office Action must disclose persuasive evidence with a detailed analysis to demonstrate the reasoning as to why the specification would not enable one of ordinary skill in the art to practice the invention without undue experimentation.

There is clearly sufficient disclosure in the specification as to how the method may be practiced. It is reasonable to conclude that the specification does teach how to practice the method according to the full extent claimed. The Office Action has not set forth a reasonable explanation why the rejected claims are not enabled by the specification and accordingly, Applicant respectfully traverses the rejection and requests that it be withdrawn.

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Claims 1-7, 9, 21, 23, and 24 are rejected under 35 U.S.C. § 112, second paragraph, as purportedly indefinite. In this rejection, the Office Action again asserts the terms and phrase "natural biotin", "linkers", "a trifunctional crosslinking moiety" and "derivatives or fragments thereof having essentially the same binding function to biotin as avidin or streptavidin" are not adequately defined by the specification. Applicants again respectfully traverse.

Applicants again point out the claims have been amended to refer to "biotin" instead of "natural biotin." Moreover, as explained above, those of skill in the art readily understand what biotin is. Those of ordinary skill in the art also would readily know what avidin and streptavidin are, and how these molecules interact with biotin and what is intended by "derivatives or fragments thereof having essentially the same binding function to biotin as avidin or streptavidin." In other words, the metes and bounds of the claims encompass those derivatives and fragments of avidin and streptavidin that have essentially

the same binding function to biotin as does avidin or streptavidin. This is readily ascertainable by those of ordinary skill in the art.

The term "linker" has further been defined in the claims. Furthermore, Applicants again submit that those of ordinary skill in the art would readily understand what is intended and encompassed by the terms "linkers" and "a trifunctional crosslinking moiety."

In view of the above remarks, Applicants submit that this rejection is overcome and request it be withdrawn.

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Claims 1-7, 9, 21, 23, and 24 are rejected under 35 U.S.C. § 102(b) as purportedly anticipated by Wilbur et al. (WO 97/29114). Applicants traverse this rejection.

Independent claim 1 (from which the other claims all ultimately depend) concerns a method for conditioning a multi-purpose extracorporeal device. The method uses a reagent comprising two biotins, where the biotins are separated 20Å to 60Å from each other. The recited distance between the biotins ensures that the two biotins bind to one and the same biotin binding molecule, such as avidin, thereby generating a device having a stable and organized network in which all the biotin binding molecules, such as avidin, are covered by biotin molecules. Hence, the net-work consists of units of one avidin having two reagents attached, i.e., each reagent being connected to avidin by the two biotin molecules. The reagent has one free toxic binding molecule. The toxic binding molecule and the two biotins are connected to each other by a trifunctional cross-linking moiety and linkers. By such a method, a device is produced, which has the ability to solve a number of specific problems.

The claimed method includes passing a solution containing a reagent, represented by a specific formula as discussed above, through a device containing biotin binding molecules selected from the group consisting of avidin, streptavidin or derivatives or fragments thereof having essentially the same binding function to biotin as avidin or

streptavidin. The reagent through the two biotins is bound to the one biotin binding molecule of device. Moreover, the device is converted from a biotin binding to a toxic material binding device.

Wilbur teaches how to produce biotinylated reagents. Additionally, Wilbur et al. discloses different biotin dimers, biotin trimers and biotin multimers, which by their structure may be used to amplify compounds, (i.e. by providing polymerization of biotin-binding proteins (see page 35, line 15)). Wilbur neither teaches nor fairly describes a method for producing a reagent having two biotins connected to a trifunctional cross-linking moiety to which a toxic binding moiety is linked, wherein the distance between the biotin dimers is important and should be 20Å to 60Å. In fact, Wilbur specifically teaches it is important that the distance between the two biotin moieties be long enough (>15Å) to bind two proteins, but short enough (<20Å), such that two biotins will not bind the same avidin or streptavidin molecule (see page 29, line 15-17).

In addition, Wilbur neither teaches nor fairly describes preparing a multipurpose device by using a single step of conditioning an avidin/streptavidin device, which can remove endogenous toxic compounds or avidin/streptavidin compounds. Wilbur provides no guidance for producing an extracorporeal device or how to apply the various biotin multimers in any technology even remotely related to extracorporeal blood treatment. In the Office Action, it was asserted "Wilbur et al teach the instant trifunctional linking compounds as useful for adsorbing to a column for extracting various compounds". However, the cited lines of Wilbur read as follows "Biotinylated nucleic acids have been widely used. Purification techniques such as affinity chromatography frequently employs biotinylated materials." These sentences are part of the Background of the Invention section and do not refer to the claimed invention but to a well-known fact that biotinylated materials are used in chromatography.

In view of the above remarks, Applicants submit that Wilbur fails to teach or fairly describe each and every feature of the method of independent claim 1. Hence, Wilbur cannot anticipate the claims. Withdrawal of this rejection is thus respectfully requested.

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Claims 1-7, 9-11 and 21-24 are rejected under 35 U.S.C. § 103(a) as purportedly obvious based on Norrgren et al. (J. Nuclear Med. 1993) and Chen et al. (J. Nuclear Med. 1997) in view of Wilbur et al. Applicants traverse.

Applicants again provide the following additional background information to help to explain the invention. The presently claimed method addresses the problem of developing multipurpose extracorporeal blood clearance devices to enable the same technology platform (an avidin/streptavidin coated device) to be utilized in order to produce various specific devices through a one-step conversion which could occur at the site of treatment. This technology will have a major impact on the availability of such specific devices at the hospital, since the time and effort to produce, test and register each specific device is a daunting task.

Furthermore, the present invention solves a number of problems related to the technical features of such devices. The first problem is related to the stability of the device. Although the binding affinity of the biotin-avidin/streptavidin interaction is extremely high, the affinity does decrease substantially when avidin is immobilized. In the present invention the fact that two biotin moieties are used for binding one avidin improves the stability of the resulting device.

The second problem is to secure that the non-toxic compounds (i.e. endogenous biotin), are not cleared from the blood during the use of the device. It is solely the desired toxic compounds that should be removed from the blood. The third problem is that the components within the device should resist stream sterilization or irradiation. This

problem is solved because saturation of avidin with biotin enhances the stability of the avidin molecule with respect to denaturation conditions, such as elevated temperature.

The above three problems are solved by the use of the invented method which produces a reagent having two biotins being separated by 20Å to 60Å from each other connected to a trifunctional cross-linking group. As explained above, using a distance of 20Å to 60Å, results in one avidin molecule being connected to two biotins. Thereby all the avidins within the device will be covered by biotin and no endogenous biotin will be removed from the blood upon use. In addition, the stability of the resulting device is maintained during sterilization of the device. Additionally, a homogeneous network can be created by the use of such a reagent, since the distance of 20Å to 60Å prevents the reagent from binding to two different avidins.

The fourth problem to be solved is that the resulting device in its different conditioning forms enables the removal of toxic endogenous compounds circulating in a mammal as well as exogenous toxic compounds previously administered to the patient. This is solved by the attachment of a toxic binding moiety to the two trifunctional cross-linking groups. The toxic binding moiety may be an antigen, antibody or biotin. The present invention also solves the problem of retaining the haemocompatibility features of the original device after conditioning which is crucial for devices where whole blood are processed. This is due to the fact that although multi-attachment of the immobilized reagent occurs, no cross-linking of the extracorporeal matrix occurs. The importance of this feature can only be fully appreciated by someone with expert knowledge in designing such devices, which limits the group to the inventors of this invention.

Norrgren teaches how to use a specific extracorporeal immunoadsorption device to remove biotinylated radio labeled antibodies from the blood by passing blood containing a biotinylated antibody through an avidin column. In Norrgren's device, the biotinylated antibody binds to the avidin column. Contrary to the assertion in the Office Action,

Norrgren does not "teach the useful nature of extracorporeal extraction of various specific adsorption columns" but the use of a specific avidin coated column for the removal of biotinylated radiolabeled antibodies which has previously been administered to the animal and where the extracorporeal setting is based on processing of blood plasma contrary to that of whole blood.

At page 448, column 2, Norrgren teaches that prior art has used conventionally radiolabeled antibodies to treat tumors. Moreover, the method in that particular paper is to use a biotinylated radio labeled antibody to enable the possibility of removing the antibodies which have not been bound to the tumors (i.e. the removal is facilitated through the biotin molecule). Norrgren neither teaches nor fairly suggests a method for producing a toxic binding device which could be used to remove toxic compounds which are not connected to biotin, which endogenous toxic compounds are not.

In fact, a person faced with that particular problem would not find the solution by combining Norrgren and Wilbur. Norrgren et al., teaches an improved method of using biotinylated radio labeled antibodies and nothing about removal of non-biotinylated compounds whatsoever. Norrgren does not even mention the problem of removing endogenous toxic compounds. Wilbur, as discussed above, is faced with other problems in how to create biotin molecules which do not bind to one and the same avidin to manage to create a complex. Nothing in either document mentions a method which produces a reagent having a trifunctional cross-linked moiety having biotin dimer, wherein the distance of the biotins is 20Å to 60Å, and a toxic binding moiety. Nothing is mentioned of the need for such a reagent or what to use such a reagent for, such as to create a device. A device, which solves problems of adsorption of endogenous components as well as enhances the stability of the avidin molecule and at the same time enables the possibility of removing non-biotinylated toxic compounds from blood.

Applicants now turn to Chen. Applicants initially wish to point out that Chen and Norrgren are members of the same scientific group. Moreover, Chen compares the use of an avidin device with a method in which a biotinylated antibody as well as avidin is injected into a mammal. This results in overloading of the liver compared to the case when no avidin is used. The method of Chen is applicable to biotinylated components and not to non-biotinylated components. Therefore, the same comments with respect to Norrgren combined with Wilbur are applicable to Chen combined with Norrgren.

One of ordinary skill faced with the above-mentioned problems of developing a method for making a device which solves all of the above-mentioned problems, would find no guidance by combining Norrgren, Chen, and Wilbur. Even when these documents are combined, one of ordinary skill would not arrive at the presently claimed method. This is because nothing in the cited patents gives any directions how to develop a method, wherein an avidin device is conditioned in such a way that the device contains a specific di-biotin reagent attached to the biotin binding moiety, such as avidin. The reagent is attached to solely one avidin and at the same time all the avidins are covered by biotin molecules. This is achieved by using a distance between the two biotins of 20Å to 60Å. Applicants again stress that Wilbur teaches it is important that the distance between the two biotin moieties be long enough (>15Å) to bind two proteins, but short enough (<20Å), such that two biotins will not bind the same avidin or streptavidin molecule (see page 29, line 15-17). This teaches a person skilled in the art away from using a distance that is larger, such as the claimed distance, in any kind of biotin dimer in order to avoid cross-linking between avidin/streptavidin and biotin.

In view of the above remarks, Applicants respectfully submit that this rejection is overcome. Reconsideration and withdrawal of the rejection is thus requested.

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Applicants respectfully submit that this Amendment and the above remarks obviate the outstanding rejections in this case, thereby placing the application in condition for immediate allowance. Allowance of this application is earnestly solicited.

If any fees under 37 C.F.R. §§ 1.16 or 1.17 are due in connection with this filing, please charge the fees to Deposit Account No. 02-4300; Order No. 033700.004.

If an extension of time under 37 C.F.R. § 1.136 is necessary that is not accounted for in the papers filed herewith, such an extension is requested. The extension fee should be charged to Deposit Account No. 02-4300; Order No. 033700.004.

Respectfully submitted,

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